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Childhood trauma-related alterations in brain function during a Theory-of-Mind task in schizophrenia

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ABSTRACT

Childhood trauma is a risk factor for schizophrenia that affects brain functions associated with higher cognitive processes, including social cognition. Alterations in Theory-of-Mind (ToM), or mentalizing skills, are a hallmark feature of schizophrenia, and are also evident in individuals exposed to childhood trauma. However, the impact of childhood trauma exposure on brain function during social cognition in schizophrenia remains unclear. We thus examined the association between childhood trauma and brain function during the performance of a ToM task in 47 patients diagnosed with schizophrenia or schizoaffective disorder. All participants completed the Childhood Trauma Questionnaire (CTQ) and underwent functional magnetic resonance imaging while performing an established visual-cartoon affective ToM task. Whole-brain multiple regression analysis was performed on ToM-related brain activation, with CTQ total score as regressor of interest, while accounting for the effects of age, sex, diagnosis, symptom severity, behavioural performance, intelligence and medications levels. First, using a small-volume correction approach within a mask made of key regions for ToM [including bilateral temporo-parietal junctions (TPJ), medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC)/precuneus], total CTQ scores were positively associated with activation of the PCC/precuneus. Second, exploratory analyses for the rest of the brain (i.e., ROIs masked-out), revealed a positive association between trauma exposure and activation of the dorsomedial prefrontal cortex (dmPFC), and a negative association with activation of the anterior section of the TPJ. These results suggest that childhood trauma exposure may, at least partially, contribute to functional alterations of brain regions essential for effective mental state inference in schizophrenia.

1. Introduction

Theory-of-Mind (ToM), or 'mentalizing', involves higher-order social cognitive processes to facilitate accurate understanding of others' thoughts, emotions and intentions (i.e., mental states), which in turn facilitates adaptive social behaviour (Wimmer and Perner, 1983). Deficits in ToM are pervasive features of schizophrenia (Bora et al., 2009) that are known to impact social functioning (Couture et al., 2006) in both acute (Bora et al., 2009) and remitted patients (Sprong et al., 2007). Effective ToM processes are critically dependent on the functional integrity of 'affective ToM' and 'cognitive ToM' networks (Abu-Akel and Shamay-Tsoory, 2011). The temporo-parietal junction (TPJ), the posterior cingulate cortex (PCC)/precuneus and the superior temporal sulcus (STS) are common to both networks; however, the 'affective ToM' network also involves the ventromedial prefrontal cortex (vmPFC)/orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (vlPFC), ventral anterior cingulate cortex (vACC), ventral striatum, amygdala, temporal poles, while the 'cognitive ToM' network involves the dorsomedial prefrontal cortex (dmPFC), dorsolateral prefrontal cortex (dlPFC), dorsal ACC (dACC) and the dorsal striatum (Abu-Akel and Shamay-Tsoory, 2011). A recent meta-analysis of neural activation in schizophrenia during ToM tasks (including 9 studies comparing 133 schizophrenia patients to 140 healthy controls) revealed *increased* activation of the PCC, the STS and somatosensory cortices, and *decreased*

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activation of the mPFC (Sugranyes et al., 2011). Similarly *increased* activation in the PCC and the TPJ and *decreased* activation in the mPFC have been reported in unaffected first-degree relatives of patients with schizophrenia (Mohnke et al., 2016).

In non-psychotic populations, exposure to childhood trauma is commonly associated with deficits on higher cognitive processes (executive functions, working memory or emotional processes) and associated brain regions (Hart and Rubia, 2012). Importantly, alterations of social cognitive skills are evident in maltreated youths (Benarous et al., 2015; Luke and Banerjee, 2013) and ostensibly healthy adults (Germine et al., 2015), and adults with posttraumatic stress disorder (Nazarov et al., 2014). Childhood maltreatment is associated with increased *centrality* (i.e., the importance of a node in a network) of the right precuneus and the right anterior insula, and reduced importance of the left ACC, in brain networks sustaining social cognitive skills (such as emotion regulation, mental state inference, ascribing intentions or beliefs to others; Teicher et al., 2014). Consistently, increased amygdala activation has been found in trauma-exposed patients with chronic depression performing an affective ToM task (Hentze et al., 2016), consistent with similar patterns of amygdala hyper-activation reported in trauma-exposed (healthy) individuals performing a face-matching task (Dannlowski et al., 2012).

Exposure to childhood trauma is also a significant risk factor for psychosis (Green et al., 2014; Read et al., 2014) that impacts morphology and function of key brain regions for cognition in these populations. In mixed samples of psychotic disorders (i.e., comprising schizophrenia, schizoaffective disorder, and psychotic bipolar cases), exposure to sexual abuse has been associated with decreased grey matter in the left dlPFC and the ACC (Sheffield et al., 2013), while exposure to any type of childhood trauma has been associated with *increased* activation of the left inferior parietal lobule when performing a working memory task (Quidé et al., 2016). In schizophrenia, exposure to emotional neglect has been associated with reduced grey matter volume of the right dlPFC (Cancel et al., 2015), while exposure to sexual abuse and physical neglect were associated with aberrant amygdala-PCC/precuneus functional connectivity during an emotion-processing task (Cancel et al., 2016). These regions show considerable overlap with brain regions implicated in ToM performance, suggesting that trauma-exposure may contribute to brain functional alterations associated with social cognitive impairments, as previously described in schizophrenia (Mrizak et al., 2016). Despite the high prevalence of trauma exposure in schizophrenia (Larsson et al., 2013; Matheson et al., 2013) and evidence for trauma-related ToM deficits, the effects of childhood trauma on ToM brain function in schizophrenia have not yet been investigated.

We thus set out to investigate the effects of childhood trauma exposure on brain function associated with ToM processes in a sample of patients with schizophrenia and schizoaffective disorder. Specifically, we investigated the associations between exposure to childhood trauma (Bernstein et al., 2003) and brain activation (blood oxygenation level dependent signal changes) occurring during the performance of a well-characterized and robust ToM task. Unlike its extended version (Schnell et al., 2011), the two conditions version of the ToM task used here, does not distinguish between affective and cognitive ToM processes (Mohnke et al., 2014; Walter et al., 2011). We expected that childhood trauma would be associated with *increased* activation within a mask of ToM-related key regions derived from van Overwalle's meta-analysis (Van Overwalle, 2009), including bilateral TPJ, the PCC/precuneus and the mPFC. We also explored the potential associations between childhood trauma exposure and activation of brain regions outside these regions.

2. Materials and methods

2.1. Participants

All participants provided informed consent according to procedures approved by the UNSW Human Research Ethics committees (HC12384), the South East Sydney and Illawarra Area Health Service (HREC 09/081) and St Vincent's Hospital (HREC/10/SVH/9). Participants were 47 clinical cases meeting ICD-10 criteria (W.H.O., 2008) for schizophrenia (n = 29) or schizoaffective disorder (n = 18), recruited from local area health services, the Australian Schizophrenia Research Bank (ASRB; Loughland et al., 2010) and by advertisement in the local community. Exclusion criteria included inability to communicate sufficiently in English, current neurological disorder, any history of head injuries with loss of consciousness, a diagnosis of substance abuse/dependence in the past six months, and having received electroconvulsive therapy in the previous six months.

2.2. Materials

Clinical diagnoses according to ICD-10 criteria were derived using the OPCRIT algorithm (McGuffin and Farmer, 1991) applied to interviewer ratings on the Diagnostic Interview for Psychosis (Castle et al., 2006). Current symptom severity was determined using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989), current Intellectual Quotient (IQ) levels were measured by the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), and handedness was determined using the Edinburgh Handedness Inventory (Oldfield, 1971).

Exposure to childhood trauma was measured using the short form (25 items) of the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). The CTQ is a self-report questionnaire that measures childhood (before age 12 years) trauma exposure on domains of emotional (EA), physical (PA) and sexual (SA) abuse, as well as physical (PN) and emotional (EN) neglect. For each domain, a score is calculated from 5 items, each rated with a 5-point Likert scale ranging from 1 (never true) to 5 (very often true); responses within each domain were summed, and scores within the Moderate to Extreme range (i.e., EA > 12; PA > 9; SA > 7; EN > 14; PN > 9) on any one of these domains indicates significant trauma severity (Mørkved et al., 2016; Quidé et al., 2016; Shannon et al., 2011). Due to high correlation among CTQ domains (Table 1) and because 38% of the present sample reported exposure to significant trauma severity on multiple CTQ domains (Table 2), we used the CTQ total score for focal functional brain imaging analyses.

2.3. Theory-of-Mind (ToM) task

The ToM task was developed for use in functional neuroimaging studies (Schnell et al., 2011) and demonstrates excellent reliability (0.76 < ICC < 0.82) of ToM-related brain activity (Mohnke et al., 2014). In its shortened version with two conditions, that is, a control condition and an affective ToM condition (Mohnke et al., 2014; Walter et al., 2011), it does not distinguish between affective and cognitive ToM processes and is not particularly sensitive to behavioural performance (Mohnke et al., 2014). The task employed a block-design that alternates between 8 blocks of 'ToM' and 8 blocks of 'Control' conditions (total paradigm time: 480 s). Each block comprised 4 frames: an instruction frame (6.53 s), followed by a cartoon story in three consecutive frames (22.58 s; 7.53 s per image). For the control conditions, participants counted the number of living characters in the cartoon frames and determined if there was a change (same, more or less) between frames. For the ToM condition, participants were required to report whether the protagonist's affect would be expected to have changed according to the circumstances, by specifically indicating whether the *affective state of the protagonist* would be expected to be the *same as, better, or worse than*, the previous picture in the cartoon sequence. Pictures were free of direct emotional cues such as characters' facial expressions to avoid simple activation of emotion perception networks.

Stimuli were displayed on a Philips LCD monitor at the rear of the magnet, viewed by the participant via a standard head coil mirror. A Cedrus Lumina response box was used to measure behavioural responses. All participants underwent an "offline" task training session before the fMRI data acquisition. Accuracy in the different conditions